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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/534,226	05/06/2005	Carsten Horn	A800.081	3361

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Gail Poulos
USDA ARS Office of Technology Transfer
5607 Sunnyside Avenue, RM 4-1184
Beltsville, MD 20705-5131

EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,226	HORN ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) *1-10,23,25-34 and 47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-22,24,35-46 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/06/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of Group II, claims 11-22,24,35-46 in the reply filed on 01/029/2008 is acknowledged. The traversal is on the ground(s) that according to the MPEP, the inventions must be independent *or* distinct and there must be a serious burden on the Examiner if restriction is required. This is not found persuasive because the instant application is filed under 35 USC 371. Search burden is not germane to PCT practice. Furthermore, the technologies and constructs used in Groups I and II are distinct. RMCE is necessary for Group II and not for Groups I and III. Groups I and III require an internal transposon half side useful in immobilization of the transposon and do not require the site-specific recombinase target site of Groups II and IV. Such an element is not required in Groups II and IV. Groups III and IV are drawn to methods of integration into the vertebrate genome using transposons. Transposon technology and art is divergent between vertebrates and invertebrates.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-46 are pending. Claims 1-10,23,25-34 and 47 are withdrawn. Claims 11-22,24,35-46 and 48 are under examination in the instant office action.

Claims 35-46 are examined only to the extent that they read on the elected invention, specifically methods involving invertebrates. Thus, the examined subject matter of claims 35-46 is the same as that of claims 11-22.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Germany on 11/07/2002. It is noted, however, that applicant has not filed a certified copy of the DE 10251918.8 application as required by 35 U.S.C. 119(b). As such, until the required documents are received, the effective filing date for the instant application is considered to be 11/07/2003, the filing of PCT/US03/35587.

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-22,24, 35-46 and 48 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of integrating a heritable integration of a transgene into the genome of a somatic or germ line cell of an invertebrate organism said method comprising, i) integrating a first acceptor DNA cassette into said genome by transposase-mediated integration of a first vector wherein the first vector comprises said first DNA cassette flanked on each end by first and second transposon half sides and wherein said first DNA cassette comprises heterospecific site-specific recombinase target sites flanking each end of a first marker gene and ii) exchanging said first acceptor DNA cassette for a second donor DNA cassette by recombinase-mediated site-specific recombination using a second vector comprising a second DNA cassette comprising heterospecific site-specific recombinase target sites flanking each end of an internal transposon half side followed by a second marker gene wherein said internal transposon half side and a first flanking half side form a pair of excisable transposon halfsides, does not reasonably provide enablement for any second donor vector. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the

invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

It is noted that the Examiner interprets the first mentioned cassette, above, as the acceptor as set forth in Figure 8. The second cassette is the donor as set forth at Figure 10. The method is considered to be that exemplified in Figure 7. The presence of *linotte* and additional marker genes in the vectors are considered as optional embodiments that are not necessary enabling embodiments.

Claim 11 is broad in that it encompasses an exchange step that lacks any structural limitations on the second DNA cassette. The specification teaches a highly specific structure of the second donor cassette wherein heterospecific FRT sites are used to recombine intervening marker DNA, which differs from marker DNA of the acceptor cassette, in addition to a transposon half side that is necessary to immobilize the final insertion. The specification does not teach exchange with any vector. While the internal composition of the donor cassette is not of prime importance, the claim fails to recite any structural features necessary for the claimed exchange. The claim sets forth that recombination occurs between recombinase target sites, however, it does not require the presence of target sites or specify that the target sites are heterospecific to one another such that they would be homospecific to those of the acceptor, which is necessary for a double crossover event. The lack of presence of such sites is indicated by the additional requirement in claim 17.

Claim 11 also fails to require the presence of an internal transposon half side. The specification teaches the presence of an internal transposon half side in the donor such that the final structure can be immobilized. Otherwise, the insertion can mobilize using the flanking L1 and R1 half sides. The use of the invention is in 'targeting' a gene to a desired locus that possesses favorable position effects and expression level of an inserted transgene. A mobile transposable element fails to benefit from this because if it moves to a different site in the genome, the position effects may not be so favorable and a change in transgene expression may occur. Wimmer [2005, Nature Methods, 2:580-582], who discusses the technology postfiling, discusses that transposon-mediated transgene integrations can be remobilized by the introduction of transposase or by crossreacting activities. Removal of one of the transposon ends, requiring an internal transposon half side, will stabilize the insertion (see para bridging pages 581-582). Thus, to use the invention as intended, the donor DNA cassette should be limited to that comprising an internal transposon halfside.

Furthermore, the method, as claimed, fails to 'target' an integration into the genome because the acceptor DNA is randomly integrated and the claims lack a step of identifying a selecting an integration site as a desired target.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11-22,24, 35-46 and 48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "and additional DNA sequence" is unclear in claims 1 and 35. It is not clear if the site-specific recombinase sites flank the additional DNA sequence or if the cassette comprises additional

DNA sequence. It is not clear which aspect of the claim that this phrase is intended to modify. Claims 12-22,24 depend from claim 11. Claims 36-46 and 48 depend from claim 3.

Claim 14 is unclear as it is not known whether the first cassette of claim 11 'further' comprises one site-specific recombinase target site with the recited placement or whether the claim is intended to limit the placement of 'one site-specific recombinase target site' recited in claim 11. This aspect is unclear because claim 14 recites "in-between a marker gene coding region and a promoter DNA…" which is not recited in claim 11 and lacks clear antecedent basis.

Claim 19 recites the limitation "the same homing sequence" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim or in the parent claims.

Claim 21 recites the limitation "an operable promoter of…. " in line 2. There is insufficient antecedent basis for this limitation in the claim or in the parent claims.

Claim 38 is unclear as it is not known whether the first cassette of claim 35 'further' comprises one site-specific recombinase target site with the recited placement or whether the claim is intended to limit the placement of 'one site-specific recombinase target site' recited in claim 35. This aspect is unclear because claim 38 recites "in-between a marker gene coding region and a promoter DNA…" which is not recited in claim 35 and lacks clear antecedent basis.

Claim 43 recites the limitation "the same homing sequence" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim or in the parent claims.

Claim 45 recites the limitation "an operable promoter of…. " in line 2. There is insufficient antecedent basis for this limitation in the claim or in the parent claims.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Horn and Handler, 2005, Site-specific genomic targeting in Drosophila, PNAS, 102:12483-12488.

Handler, AM et al, 2004, Post-integration stabilization of a transposon vector by terminal sequence deletion in Drosophila melanogaster, Nature Biotechnology, 22:1150-1154.

Bateman, JR et al, 2006, Site-specific transformation of drosophila via ϕC31 integrase mediated cassette exchange, Genetics, 173:769-777.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Valarie Bertoglio, Ph.D./
Primary Examiner
Art Unit 1632

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